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New Benzylpiperazine Derivatives Bearing Mono- and Bis-dialkyl Substituted 1,2,4-Triazoles

Yaseen A. Al-Soud,[1] Mohammed N. A. Qalalweh,[1]
Haitham H. Al-Sa'doni,[1] and Najim A. Al-Masoudi[2]

[1]*Department of Chemistry, College of Science, University of Al al-Bayt, Al-Mafraq, Jordan*

[2]*Formerly Fachbereich Chemie, Universität Konstanz, Postfach 5560, D-78457 Konstanz, Germany*

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ABSTRACT: *Cycloaddition of the 1-aza-2-azonia-allenes* **3** *with p-cyanobenzyl chlorides afforded, after spontaneous rearrangement, the 1,5-dialkyl-3-[4-chloromethyl)phenyl]-1*H*-[1,2,4]-triazoles* **6**. *A series of 1,5-dialkyl-1*H*-[1,2,4]-triazol-3-yl)benzyl-piperazines* **7** *and* **8** *were prepared from direct condensation of* **6** *with piperazine and N-methylpiperazine, respectively. The structures of the newly synthesized products were identified by 2D NMR spectroscopy.*
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INTRODUCTION

Several heterocycles containing piperazines residues have been described as potent chemotherapeutic agents. Recently, some compounds bearing piperazines residue were described as highly specific inhibitory of HIV-1 replication, such as bis-(indolyl)-piperazine (BHAP) [4] and trovirdine derivative [5]. Other various 1,2-dialkyl piperazines have been reported as antibacterial [6–8], antiprotozoacidal [9], antihypertensive [10,11], coronary dilators [12], H-3 antagonists [13], such as the antipsychotic agent clozapine [14], tryptase inhibitors [15,16], antiplatelet agents with antivasodialatory effect [17], sedative and tranquilizers [18], antihelminitic and antifilarial agents [19], antineoplastic agents [7,20,21], as well as antagonist of postsynaptic receptors 5-HT1A [22,23]. The pharmacological potency of such substituted piperazines, as well as the biological activity of 1,2,4-triazole analogues such as fluconazole [24] prompted us to prepare a new series of 1,4-disubtituted piperazines carrying substituted 1,2,4-triazoles and/or methyl group, as potential antitumor candidates.

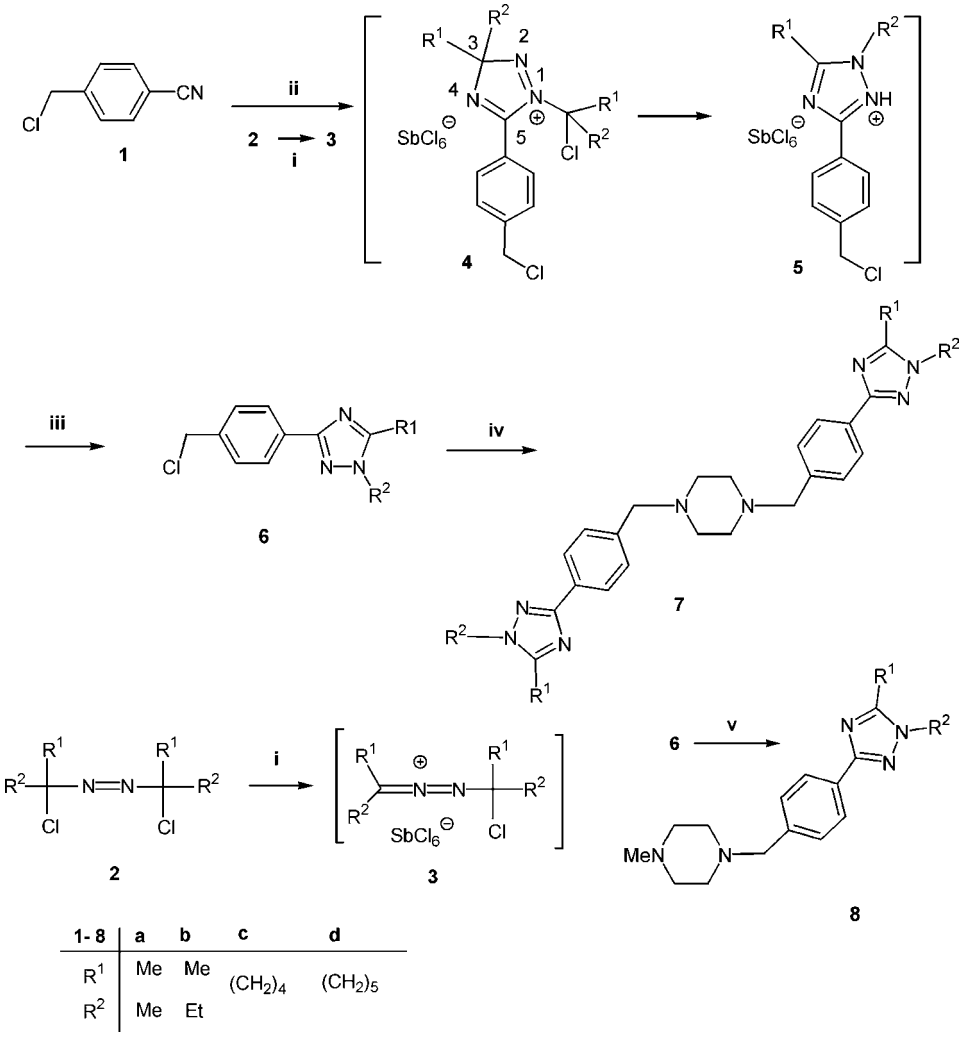
Correspondence to: Najim A. Al-Masoudi; e-mail: Najim.Al-Masoudi@gmx.de.

RESULTS AND DISCUSSION

Recently, the 4,5-dihydro-3*H*-pyrazolium salts have been synthesized from the cycloaddition of the short-lived 1-(chloroalkyl)-1-aza-2-azoniaallene hexachloroantimonates **3** [25–27] to various electron-rich alkenes in the presence of Lewis acids like $SbCl_5$; similarly numerous compounds of 1,2,4-triazoles were prepared recently in our laboratory *via* the cycloaddition of the nitrile derivatives to intermediates **3**. Such examples of our recent work are 1,2,4-triazole *C*-nucleosides [28,29], acyclic *C*-nucleosides [30], pyrimidines [31], *N*-alkylphthalimides [32], D-*manno*-pentitol-1-yl-1,2,4-triazoles [33], 1*H*-indoles as well as quinolines [34], benzotriazoles [35], 3′-triazolothymidines [36], *N*,*N*′-trisubstituted 1,2,4-triazolo-piperazines [37], and 1,2,4-triazole derivatives

of acetic acid alkylidene hydrazides [38]. In the present study, we prepared the 3-[4-(chloromethyl)-phenyl]-1,5-dimethyl-1*H*-1,2,4-triazole **6a** and **6c**, according to our reported method during the preparation of **6b** and **6d** [34], from the cycloaddition of **3** to 4-cyanobenzyl chloride **1**. Thus, the dichlorides **2** were converted, at approximately −60°C, to the salts **3** in the presence of $SbCl_5$. At −30°C, the color changed indicating that **3** underwent cycloaddition with the nitrile **1** to give the inseparable 5-[4-chloromethyl)-phenyl]-3*H*-1,2,4-triazolium hexachloroantimonates **4**. As the temperature was raised above −30°C, **4** rearranged to protonated triazole **5** by [1,2] migration [39,40] of the alkyl group (R^2) at C-3 to N-2, accompanied by elimination of the $CClR^1R^2$ group. In situ hydrolysis of **5** with aqueous $NaHCO_3$ and aqueous NH_3 afforded the triazoles **6a** and **6c** in 65 and 73% yield, respectively.

Next, condensation of **6a–d** with piperazine in the ratio of (2:1) in the presence of NaH or K_2CO_3 and DMF at 25°C for 48 h afforded, after recrystallization from the appropriate solvent, the desired products of 1,4-bis-(1,5-dialkyl-1*H*-[1,2,4]-triazol-3-ylbenzyl)-piperazines **7a–d** in 85–87% yield (Scheme 1). These compounds were identified by homo- and heteronuclear NMR spectroscopic methods, HMBC [41], and mass spectra. The ^{1}H NMR spectra of **7a–d** showed similar patterns. The CH_2-1′ appeared as singlets at δ 3.53, 3.61, 3.54, and 3.55, respectively. The two doublets at δ 7.97, 7.42 (8.2 Hz); 7.99, 7.38 (8.1 Hz); 8.00, 7.37 (7.7 Hz), and 7.97, 7.35 (8.2 Hz), respectively, were attributed for the symmetrical four aromatic protons. The alkyl groups at N-1″ and C-5″ were assigned. The ^{13}C NMR spectra of **7a–d** contained the resonance signals of the triazole carbons ring (C-3″, C-5″ of **7a,b**) and (C-2″, C-10″ of **7c,d**) at higher fields



SCHEME 1 *Reagents and conditions*: i. 2, $SbCl_5$, CH_2Cl_2, −60°C; ii. CH_2Cl_2, −60°C to 23°C; iii. $NaHCO_3$, NH_3, MeCN, 0°C, 2h; iv. piperazine, NaH or K_2CO_3; v. methylpiperazine K_2CO_3, DMF.

between δ 159.5–161.5 and δ 151.8–157.8, respectively. Due to the identical groups attached at N-1 and N-4, the carbon atoms of piperazine ring of **7a–d** appeared as broad singlets at δ 53.1, 53.1, 51.4, and 51.1, respectively. Compound **7d** was selected for this NMR study showing a $^3J_{C,H}$ between C-10″ at δ 157.8 and CH_2-5″ at δ 4.18, as well as a $^2J_{C,H}$ between Ar-quart. *C* at 138.7 and CH_2-1′ at δ 3.53. An obvious $^3J_{C,H}$ correlation was shown between C-5″ at δ 53.0 and CH_2-7″ at δ 1.77, as well. The antitumor activity is under investigation.

Similarly, the 1-(1,5-dialkyl-1*H*-[1,2,4]-triazol-3-ylbenzyl)-4-methylpiperazines **8a–d** were prepared from condensation of **6** with *N*-Me-piperazine in DMF as a solvent and K_2CO_3 for 48 h at 25°C in 28, 33, 40, 29% yields, respectively (Scheme 1).

EXPERIMENTAL [28–37]

*Preparation of 1,5-dialkyl-3-[4-chloromethyl)-phenyl]-1H-[1,2,4]-triazoles (**6**)*

To a stirred, cooled (−60°C) solution of **2** (5.0 mmol) and **1** (0.76 g, 5.0 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise a solution of $SbCl_5$ (4.20 g, 5.0 mmol) in dry CH_2Cl_2 (20 mL). The solution was left with stirring at −60°C for 1 h, then at 0°C for 1 h, and finally at 23°C for 10 min, followed by addition of pentane (50 mL). The precipitated solid was dissolved in CH_3CN (40 mL), cooled to 0°C followed by addition of an aqueous solution of $NaHCO_3$ (2.55 g, 30 mmol in 30 mL of water) and NH_3 solution (2 mL). The mixture was stirred at room temperature for 2 h, then the organic solvent was evaporated and the residue was extracted with $CHCl_3$ (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated to dryness and the residue was recrystallized from petroleum ether.

*3-[4-(Chloromethyl)phenyl]-1,5-dimethyl-1H-1,2,4-triazole (**6a**).* From **2a** (0.92 g). Yield: 0.72 g (65%); mp 150–155°C. ^{1}H-NMR ($CDCl_3$): δ 8.03 (d, 2H, J = 8.5 Hz, Ar); 7.43 (s, 2H, J = 8.4 Hz, Ar); 4.60 (s, 2H, CH_2-1′); 3.83 (s, 3H, N-Me); 2.49 (s, 3H, C_5-Me). ^{13}C-NMR ($CDCl_3$): δ 159.7 (C-3″); 152.9 (C-5″); 139.6, 128 (Ar-2 × C), 129.3 (Ar-2 × C); 127.8 (Ar-C); 126.4 (Ar-C); 45.9 (C-1′); 35.2 (N-CH_3); 11.7 (C_5-*CH_3*). Anal. calc. for $C_{11}H_{12}ClN_3$ (221.69): C, 59.60; H, 5.46; N, 18.95. Found: C, 59.31; H, 5.32; N, 18.73; MS: *m/z* (%) (EI) 220/222 (80).

*2-[4-(Chloromethyl)phenyl)]-5,6,7,8-tetrahydro-[1,2,4]-triazolo[1,5-a]pyridine (**6c**).* From **2c** (1.18 g). Yield: 0.90 g (73%); mp 110–115°C. ^{1}H-NMR ($CDCl_3$): δ 8.12 (d, 2H, J = 8.0 Hz, Ar); 7.47 (s, 2H, J = 8.0 Hz, Ar); 4.18 (t, 2H, J = 6.0 Hz, CH_2-5″); 4.27 (s, 2H, CH_2-1′); 3.28 (t, 2H, J = 6.1 Hz, CH_2-6″); 2.20 (m, 2H, CH_2-7″); 2.07 (m, 2H, CH_2-8″). ^{13}C-NMR ($CDCl_3$): 153.9 (C-2″); 152.1 (C-10″); 140.8, (Ar-C); 129.1 (Ar-2 × C); 128.7 (Ar-C); 127.3 (Ar-2 × C); 47.99 (C-5″); 45.3. (C-1′); 21.9 (C-7″); 21.7 (C-6″); 18.3 (C-8″). Anal. calc. for $C_{13}H_{14}ClN_3$ (247.72): C, 63.03; H, 5.70; N, 16.96. Found: C, 62.82; H, 5.61; N, 16.67; MS: *m/z* (%) (EI) 246/248 (85).

*Preparation of 1,4-bis-[(1,5-dialkyl-1H-[1,2,4]-triazol-3-yl)benzyl]-piperazines (**7**)*

To a solution of piperazine (0.086 g, 1.00 mmol) in DMF (7 mL) was stirred K_2CO_3 (0.22 g, 2.10 mmol) and stirred for 3 min at 25°C, followed by addition of **6** (2.10 mmol). After stirring at 25°C for 48 h, the solvent was evaporated to dryness and the residue was partitioned between CH_2Cl_2 (40 mL) and water (20 mL) and the organic layer was dried (Na_2SO_4), filtered, and evaporated to dryness. The residue was stirred with petroleum ether and filtered, dried to give **7** as a pure solid.

*1,4-Bis-[(1,5-dimethyl-1H-[1,2,4]-triazol-3-yl)-benzyl]-piperazine (**7a**).* From **6a** (0.46 g). Yield: 0.82 g (85%); mp 250–255°C, decomp. at 267°C. ^{1}H-NMR ($CDCl_3$): δ 7.97 (d, 2H, J 8.2 Hz, Ar); 7.42 (s, 2H, J 8.2 Hz, Ar); 3.84 (s, 3H, N-Me); 3.53 (s, 2H, CH_2-1′); 2.49 [br s, 11H, 4 × (CH_2) *of piperazine*; C_5-Me]. ^{13}C-NMR ($CDCl_3$): δ 161.5 (C-3″); 152.7 (C-5″); 139.1, 129.9 (Ar-2 × C), 129.3 (Ar-2 × C); 127.3 (Ar-C); 125.9 (Ar-C); 62.8 (C-1′); 53.1 (4 × C-*piperazine*); 35.1 (N-CH_3); 11.8 (C_5-*CH_3*). Anal. calc. for $C_{26}H_{32}N_8$ (456.59): C, 68.39; H, 7.06; N, 24.54. Found: C, 67.91; H, 6.89; N, 24.48; MS: *m/z* (%) (EI) 456 (90).

*1,4-Bis-(1-ethyl-5-methyl-1H-[1,2,4]-triazol-3-yl)-benzyl]-piperazine (**7b**).* From **6b** (0.49 g). Yield: 0.86 g (85%); mp 200–205°C. ^{1}H-NMR ($CDCl_3$): δ 7.99 (d, 2H, J = 8.1 Hz, Ar); 7.38 (d, 2H, J 8.1 Hz, Ar); 4.14 (q, 2H, J = 7.0 Hz, *CH_2*CH_3); 3.81 (s, 3H, *N*-Me); 3.61 (s, 2H, CH_2-1′); 2.59 [br s, 8H, 4 × (CH_2) *of piperazine*]; 1.48 (t, 3H, CH_2*CH_3*). ^{13}C-NMR ($CDCl_3$): δ 160.6 (C-3″); 151.8 (C-5″); 139.0, 130.1, 129.3 (4 × C); 127.8, 125.9 (2 × C); 62.8 (C-1′); 53.1 (4 × C-piperazine); 43.3 (*CH_2*CH_3); 14.1 (CH_2*CH_3*); 11.8 (C_5-Me). Anal. calc. for $C_{28}H_{36}N_8$ (484.64): C, 69.39; H, 7.49; N, 23.12. Found: C, 69.02; H, 7.34; N, 22.95; MS: *m/z* (%) (EI) 484 (80).

*1,4-Bis-[(5,6,7,8-tetrahydro-1H-[1,2,4]triazolo-[1,5-a]pyridin-2-yl)benzyl]-piperazine (**7c**).* From **6c** (0.52 g). Yield: 0.90 g (85%); mp 270–275°C, decomp.

at 315°C. ^{1}H-NMR ($CDCl_3$): δ 8.00 (d, 2H, $J = 7.7$ Hz, Ar); 7.37 (d, 2H, $J = 7.7$ Hz, Ar); 4.18 (t, 2H, $J = 6.0$ Hz, CH_2-5″); 3.54 (s, 2H, CH_2-1′); 2.97 (t, 2H, $J = 6.0$ Hz, CH_2-6″); 2.51 [br s, 8H, 4 × (CH_2) *of piperazine*]; 2.09 (m, 2H, CH_2-7″); 2.00 (m, 2H, CH_2-8″). ^{13}C-NMR ($CDCl_3$): δ 159.5 (C-2″); 151.5 (C-10″); 137.4, 130.0 (Ar-2 × C); 127.7, 127.6 (Ar-2 × C); 124.4 (Ar-2 × C); 61.2 (C-1′); 51.4 (4 × C-piperazine); 45.4 (C-5″); 22.1 (C-7″); 21.3 (C-6″); 18.9 (C-8″). Anal. calc. for $C_{30}H_{36}N_8$ (508.67): C, 70.84; H, 7.13; N, 22.03. Found: C, 70.62; H, 6.97; N, 21.74; MS: *m/z* (%) (EI) 508 (50).

*1,4-Bis-[(6,7,8,9-tetrahydro-5H-[1,2,4]triazolo-[1,5-a]azepin-2-yl)benzyl]-piperazine (***7d***).* From **6d** (0.55 g). Yield: 0.98 g (87%); mp 280–285°C. ^{1}H-NMR ($CDCl_3$): δ 7.97 (d, 2H, $J = 8.2$ Hz, Ar); 7.35 (d, 2H, $J = 8.2$ Hz, Ar); 4.29 (t, 2H, $J = 5.2$ Hz, CH_2-5″); 3.53 (s, 2H, CH_2-1′); 2.97 (t, 2H, $J = 6.4$ Hz, CH_2-6″); 2.49 [br s, 8H, 4 × (CH_2) *of piperazine*]; 1.87 (t, 2H, $J = 7.5$ Hz, CH_2-8″); 1.80 (m, 2H, CH_2-9″); 1.77 (t, 2H, $J = 5.2$ Hz, CH_2-7″). ^{13}C-NMR ($CDCl_3$): δ 159.5 (C-2″); 157.8 (C-10″); 138.7, 129.3 (Ar-2 × C); 129.1 (Ar-C); 127.3 (Ar-C); 125.8 (Ar-2 × C); 62.8 (C-1′); 53.0 (C-5″); 51.1 (C-piperazine); 30.3 (C-7″); 27.5 (C-6″); 27.4 (C-9″); 25.0 (C-8″). Anal. calc. for $C_{32}H_{40}N_8$ (536.7): C, 71.61; H, 7.51; N, 20.88. Found: C, 71.40; H, 7.39; N, 19.54; MS: *m/z* (%) (EI) 536 (45).

*Preparation of 1-[(1,5-dialkyl-1H-[1,2,4]-triazol-3-yl)benzyl]-4-methylpiperazines (***8a,b,d***)*

To a solution of methylpiperazine (0.20 g, 2.00 mmol) in DMF (3 mL) at ∼ −10°C was stirred with NaH (0.08 g, 2.00 mmol) for 15 min, followed by addition of **6** (2.00 mmol). After stirring for 3 h at −10°C, and for 48 h at 25°C, the solvent was evaporated to dryness and the residue was partitioned between CH_2Cl_2 (50 mL) and water (25 mL) and the organic layer was dried (Na_2SO_4), filtered, and evaporated to dryness. The residue was taken by petrolium ether to give **8** as a pure solid.

*1-[(1,5-Dimethyl-1H-[1,2,4]-triazol-3-yl)benzyl]-4-methylpiperazine (***8a***).* From **6a** (0.44 g). Yield: 0.16 g (28%); mp 170–174°C. ^{1}H-NMR ($CDCl_3$): δ 8.00 (d, 2H, *J* 7.6 Hz, Ar); 7.42 (s, 2H, *J* 7.6 Hz, Ar); 3.78 (s, 3H, N-*Me-triazole*), 3.50 (s, 2H, CH_2-1′); 2.50 [br s, 8H, 4 × (CH_2) *of piperazine*]; 2.37 (br s, 6H, N-*Me-piperazine*, $C_{5'}$-Me]. ^{13}C-NMR ($CDCl_3$): δ 160.5 (C-3′); 153.0 (C-5′); 138.6, 130.3 (Ar-2 × C), 129.2 (Ar-2 × C); 126.3 (Ar-C); 125.9 (Ar-C); 61.6 (C-1′); 53.6; 52.0 (4 × C-*piperazine*); 43.4 (N-*Me-piperazine*); 35.2 (N-Me); 11.8 ($C_{5'}$-*Me*). Anal. calc. for $C_{16}H_{23}N_5$ (285.4): C, 67.34; H, 8.12; N, 24.54. Found: C, 66.96; H, 8.04; N, 24.28; MS: *m/z* (%) (EI) 285 (50).

*1-[(1-Ethyl-5-methyl-1H-[1,2,4]-triazol-3-yl)-benzyl]-4-methylpiperazine (***8b***).* From **6b** (0.46 g). Yield: 0.20 (33%); mp 78–80°C. ^{1}H-NMR ($CDCl_3$): δ 7.93 (d, 2H, $J = 8.1$ Hz, Ar); 7.30 (s, 2H, $J = 8.1$ Hz, Ar); 4.10 (q, 2H, $J = 7.1$ Hz, N-CH_2CH_3); 3.45 (s, 2H, CH_2-1′); 2.48 [br s, 8H, 4 × (CH_2) *of piperazine*]; 2.42 (s, 3H, N-*Me-piperazine*), 2.29 (s, 3H, $C_{5'}$-Me); 1.40 (t, 3H, N-CH_2CH_3). ^{13}C-NMR ($CDCl_3$): δ 160.5 (C-3′); 151.9 (C-5′); 138.7, 130.2 (Ar-2 × C), 129.3 (Ar-2 × C); 126.0 (Ar-C); 125.9 (Ar-C); 62.7 (C-1′); 54.9, 52.6 (4 × C-*piperazine*); 44.2 (*N-Me-piperazine*); 43.4 (C_5-CH_2CH_3); 15.2 (C_5-CH_2CH_3); 11.9 ($C_{5'}$-CH_3). Anal. calc. for $C_{17}H_{25}N_5$ (299.4): C, 68.19; H, 8.42; N, 23.39. Found: C, 67.87; H, 8.31; N, 23.10; MS: *m/z* (%) (EI) 299 (95).

*1-[(5,6,7,8-Tetrahydro-1H-[1,2,4]triazolo[1,5-a]-pyridin-2-yl)benzyl]-4-methylpiperazine (***8c***).* To a suspension of methylpiperazine (0.20 g, 2.00 mmol) in EtOH (10 mL) was added Na_2CO_3 (0.21 g, 2.00 mmol), followed by addition of **6c** (0.50 g, 2.00 mol). After stirring at 25°C for 48 h, the solvent was evaporated to dryness, and the residue was worked-up as in 'method a' to give **8c** (0.25 g, 40%), as a yellow solid; mp 250–254°C. ^{1}H-NMR ($CDCl_3$): δ 7.99 (d, 2H, $J = 8.0$ Hz, Ar); 7.37 (d, 2H, $J = 8.0$ Hz, Ar); 4.18 (br s, 2H, CH_2-9″); 3.53 (s, 2H, CH_2-1′); 2.96 (br s, 2H, CH_2-6″); 2.51 [br s, 8H, 4 × (CH_2) *of piperazine*]; 2.39 (s, 3H, N-*Me-piperazine*), 2.09 (m, 2H, CH_2-7″); 2.01 (m, 2H, CH_2-8″). ^{13}C-NMR ($CDCl_3$): δ 161.1 (C-2″); 153.0 (C-9″); 139.7, 130.2 (Ar-2 × C); 129.3 (Ar-2 × C); 126.0 (Ar-2 × C); 62.8 (C-1′); 53.0, 51.5 (4 × C-*piperazine*); 45.2 (N-*Me-piperazine*); 45.3 (C-5″); 23.6 (C-7″); 22.9 (C-6″); 20.5 (C-8″). Anal. calc. for $C_{18}H_{25}N_8$ (311.4): C, 69.42; H, 8.09; N, 22.49. Found: C, 69.11; H, 7.89; N, 22.05; MS: *m/z* (%) (EI) 311 (65).

*1-[(6,7,8,9-Tetrahydro-5H-[1,2,4]triazolo[1,5-a]-azepin-2-yl)benzyl]-4-methylpiperazine (***8d***).* From **6d** (0.52 g). Yield: 0.19 g (29%); mp 111–113°C. ^{1}H-NMR ($CDCl_3$): δ 8.0 (d, 2H, $J = 8.0$ Hz, Ar); 7.35 (s, 2H, $J = 8.0$ Hz, Ar); 4.30 (m, 2H, CH_2-10″); 3.55 (s, 2H, CH_2-1′); 3.02 (t, 2H, $J = 6.5$ Hz, CH_2-6″); 2.59 [br s, 8H, 4 × (CH_2) *of piperazine*]; 2.38 (s, 3H, N-*Me-piperazine*); 1.95 (m, 2H, CH_2-8″); 1.88 (m, 2H, CH_2-9″); 1.78 (m, 2H, CH_2-7″). ^{13}C-NMR ($CDCl_3$): δ 159.4 (C-2″); 157.9 (C-10″); 139.7, 130.6 (Ar-2 × C); 129.3 (Ar-2 × C); 126.0 (Ar-2 × C); 62.2 (C-1′); 54.9, 52.9 (4 × C-*piperazine*); 51.2 (C-5″), 44.6 (N-*Me-piperazine*); 30.4 (C-7″); 27.6 (C-6″); 27.4 (C-9″); 25.0 (C-8″). Anal. calc. for $C_{19}H_{27}N_5$ (325.4):

C, 70.12; H, 8.36; N, 21.52. Found: C, 69.89; H, 8.18; N, 21.18; MS: *m/z* (%) (EI) 325 (98).

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